Office of
Agricultural
Biotechnology

Minutes

Agricultural Biotechnology Research Advisory Committee

September 22-23, 1988

Document No. 88-03

U.S. DEPARTMENT OF AGRICULTURE

AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE

MINUTES OF MEETING

September 22-23, 1988

CALL TO ORDER AND APPROVAL OF AGENDA AND MINUTES

Dr. Bennie Osburn, Chair, convened the third meeting of the Agricultural Biotechnology Research Advisory Committee (ABRAC) on September 22, 1988 in Room 104-A of the U.S. Department of Agriculture (USDA) Administration Building, 14th and Independence Avenue, S.W., Washington, D.C. The meeting was open to the public.

Members present included:

Bennie Osburn (Chair), University of California, Davis, CA;
Harold Hafs, Merck, Sharp and Dohme, Rahway, NJ;
John Gorham, Agricultural Research Service/Washington State University, Pullman, WA;
Ann Sorensen, American Farm Bureau Federation, Park Ridge, IL;
Fred Gould, North Carolina State University, Raleigh, NC;
Frank Whitmore, Ohio State University, Wooster, OH;
Nicholas Frey, Pioneer Hi-Bred International, Des Moines, IA;
John Kemp, New Mexico State University, Las Cruces, NM;
Sue Tolin, Virginia Polytechnic Institute and State University, Blacksburg, VA;
Rodney Bothast (Vice-Chair), Agricultural Research Service, Peoria, IL;
Edward Korwek, Hogan and Hartson, Washington, DC;
Anne Hollander, The Conservation Foundation, Washington, DC;
Alvin Young (Executive Secretary), USDA Office of Agricultural Biotechnology.

Alternates in attendance included:
Thomas Wagner, Ohio University, Athens, OH;
Ronald Sederoff, North Carolina State University, Raleigh, NC;
Anne Vidaver, University of Nebraska, Lincoln, NE.

The roster of the Committee is included as Appendix A.

USDA Office of Agricultural Biotechnology (OAB) staff present included: Daniel Jones, Marti Asner, Michael Olexa, Fred Kuchler, Althaea Langston, Martha Steinbock, Phillip O'Berry, Eva Russnak, Elsie Brown, Graham Purchase and David MacKenzie.

Others present for all or part of the meeting included:

Orville Bentley, USDA Assistant Secretary, Science and Education
Jeffrey Fox, Bio/Technology
Richard Parry, USDA, Agricultural Research Service
T. R. Wilkinson, RICOP, North Dakota State University
Jonathan Harsch, Agridata News Service
Jane Rissler, National Wildlife Federation
Frank Serdy, Monsanto
Robert Zimbelman, American Society of Animal Scientists
Rudy Wodzinski, University of Central Florida
Janet Shoemaker, American Society for Microbiology
Edward Raleigh, E. I. DuPont de Nemours & Co.
Gary Weber, USDA, Extension Service
Paul Stern, University of Florida
David Giamporcaro, McDermott, Will and Emery
John Irwin, National Institutes of Health
Judith Weis, National Science Foundation
Alan Goldhammer, Industrial Biotechnology Association
Keith Belton, American Chemical Society
Bruce L. Umminger, State Department
James H. Davis, Crop Genetics
Lowell Frobish, Auburn University

Dr. Osburn recognized Dr. Orville Bentley, the Assistant Secretary for Science and Education. Dr. Bentley welcomed the Committee members and thanked them for their efforts in the difficult task of developing research guidelines. He reminded the Committee members that there is a great deal of interest in their deliberations and he offered his personal assistance if the need arises.

Dr. Young suggested two changes in the agenda: that Dr. MacKenzie's comments on the Agricultural Biotechnology Handbook for Field Testing (hereinafter referred to as the Handbook) be placed after those of the other reviewers; and that the items under Other Business, "Confidential Business Information" and "Environmental Assessment", be deleted since OAB was not yet ready to report to the ABRAC on these matters. The Committee approved the agenda as modified.

The Committee approved the minutes of the meetings of March 23-24, 1988 and June 23-24, 1988.

REPORTS OF THE WORKING GROUPS

Dr. Osburn asked the Chairperson of each of the Working Groups to report briefly on their deliberations.

Working Group on Definitions

Dr. Korwek reported that the Working Group on Definitions met prior to the other working groups and developed a number of definitions related to biotechnology research despite some uncertainty as to how exactly they would be used. Thus, some terms developed by the Definitions Working Group might have to be redefined and new terms might require definitions because of their use in the Guidelines. He explained that the Working Group on Definitions had opted to work from definitions which were accepted and widely used by other U.S. Government agencies. He stated that although some Working Group members were reluctant to do so, the Working Group had defined the term "biotechnology" very broadly, with the understanding that the areas covered by the Guidelines would be narrowed by exclusions.

Dr. Kemp added that he had agreed during the Working Group meeting to develop a definition of "weed/noxious weed". He proposed that "a weed/noxious weed is a plant which is competitive, persistent and pernicious and interferes in an undesirable manner with human activities." He noted that each state has its own definition of "weed" and that these might be used in the development of the Guidelines.

Dr. Sorensen commented that it would have been preferable if the Working Group on Definitions had met after the other two Working Groups. She added that ABRAC would need to define "agriculture" and that the definitions developed should be reviewed to ensure that they are consistent with other regulations and guidelines.

Dr. Young noted that a definition developed for the purpose of the Guidelines might differ from regulatory definitions. Dr. Langston noted that some regulatory definitions are specified by law.

Working Group on Confinement

Dr. Purchase reported that the Working Group on Confinement had heard presentations about how the confinement issue is handled by other Government agencies. The USDA Animal and Plant Health Inspection Service (APHIS) system of permits is applicant driven, each case is considered separately and no general confinement levels have been set. The Environmental Protection Agency (EPA) has been unable to develop generally acceptable confinement levels for releases into the environment despite much effort. He added that the EPA representative at the Working Group meeting had explained that the National Institutes of Health (NIH) guidelines, like those being developed by the ABRAC, operate under contract law rather than statutory law. Thus, for NIH, penalties involve defunding rather than fines assessed by regulatory agencies.

Dr. Purchase explained that the Working Group viewed confinement as a continuum, ranging from no confinement to extreme stringency. He added that increased confinement could be achieved by increasing stringency of a single category of confinement (e.g., physical, biological, etc.) or by combining several categories. Dr. Purchase added that the section of the Handbook that deals with confinement lists examples of how different categories of confinement could be used together to increase stringency, although level five, as described in the Handbook should properly be described as containment because it does not involve release into the environment.

Dr. Frey noted a difference in approach between the Guidelines and the Working Group on Confinement. He said it may be difficult for researchers to understand where their experiments fit on a continuum of confinement.

Dr. Hafs complimented the Working Group on its efforts. He said it was important to tailor levels of confinement to levels of risk. He also noted that the examples given deal only with plants. Dr. Bothast endorsed the approach taken by the Confinement Working Group. He asked that examples be given in order to provide guidance to the Principal Investigator (PI).

Working Group on Guidelines

Dr. Tolin explained that the minutes of the Working Group were still in draft. She commented that the Working Group on the Guidelines had the most comprehensive charge, which was to reformulate the Guidelines as guidance to researchers rather than regulations. She reported that in order to meet this charge, the Working Group had shifted the format of the Guidelines to one similar to that used by NIH.

Dr. Tolin reported that the Working Group had devoted most of its efforts to developing the section on classification of experiments, and rewriting the basic purpose of the Guidelines. She noted that midway through its meeting the Working Group had heard a report from the Working Group on Definitions and that the broad definition of "biotechnology" had conditioned the approach taken in the Guidelines. Dr. Tolin also pointed out that the principles behind the categorization of experiments were based on the level of review required. She cautioned, however, that the levels of review described should not yet be correlated directly with levels of confinement because the two Working Groups had not yet had the opportunity to coordinate them.

Dr. Tolin also reported that the Working Group had reached consensus that the assessment of risk of modified organisms should be evaluated relative to the risk of the non-modified organism. She added that the Working Group had sought general principles which applied to plants,

animals, and microorganisms. She concluded by stating that the draft Guidelines produced by the Working Group would provide a starting point for ABRAC deliberations.

Dr. Sederoff stated that the philosophy of the Working Group was that human risk, ecological risk and levels of uncertainty should all be evaluated together relative to the risk of the non-modified organism. He reiterated that organisms should be evaluated, not the process by which modifications were made.

Dr. Gould noted that he was not a member of the Working Group, but from the point-of-view of a non-member, he believed that the draft Guidelines are a good working document. He concurred that it would be unwise to recommend confinement levels solely on the basis of the type of modification being carried out. He also suggested that recommendations in the Guidelines should be stated in qualified rather than absolute form.

AGRICULTURAL BIOTECHNOLOGY HANDBOOK ON FIELD TESTING

Dr. Osburn commended the editors, Dr. Purchase and Dr. MacKenzie, and OAB on the speed with which they produced the first draft of the Handbook.

Dr. Purchase reviewed the structure and format of the current draft of the Handbook for the Committee. He explained that the Handbook was designed to complement the Guidelines by providing more detailed instructions and guidance to researchers. He acknowledged, however, that the Handbook could not give detailed, step by step instructions for every possible experiment.

Dr. Purchase reported that some reviewers had commented that the word "Handbook" did not accurately describe the product and that the editors were considering several alternate terms such as "introduction," "primer", and "guidebook." He concluded by distributing a schematic representation of the material in the Handbook. This is attached as appendix B. He noted that this type of representation would be added to the Handbook to provide a "road map" for researchers.

Dr. Wagner told the Committee that he had shown the draft to a new Associate Professor at his university in order to get the reaction of a new researcher to the material presented. He reported that for this reviewer, the Handbook's biggest strength was that it compiled all the agencies involved in guiding and regulating field testing. He requested that more examples be given to assist new researchers. Dr. Wagner also questioned whether the chapter on public relations, although needed by researchers, was appropriate for this type of publication.

Dr. Kemp stated he had the same concerns as Dr. Wagner. He stated the book took too broad an approach and dealt with too many issues. He suggested that the Handbook be reorganized and some of the material, for example, the "Authorities for Biosafety" be put in appendices.

Ms. Hollander agreed with many of the other commentators adding that the Handbook is badly needed. She asked that the section on applicable requirements of other agencies be rewritten so that it would read more accurately. She also said the Handbook should explicitly mention non-funding penalties, and should contain more cross references. Ms. Hollander noted that the chapters on socio-economic implications and public relations were very important, but she believed the chapters needed to be reviewed for content and tone. She also expressed concern about the section on "Responsibilities of the Institution", particularly with regard to conflict of interest provisions during Institutional Biosafety Committee (IBC) reviews and the length of time given to institutions (30 days) to report problems to USDA.

Dr. MacKenzie reported the views on the Handbook of the Committee on Biotechnology of the National Association of State Universities and Land Grant Colleges (NASULGC) and Dr. Kenneth Gilles, Assistant Secretary for Marketing and Inspection Services. He said the reviewers had recommended changing the title, reorganizing the chapters and amending the book to better align with the Guidelines. He said the reviewers believed aiming the Handbook at the beginner researcher was correct. They further recommended that a "roadmap" schematic representation and sample forms for permit and other applications be added. Some reviewers also advocated adding a section on how to change the federal system of regulation and review. Finally, some reviewers found the Handbook to be too chatty in tone and recommended numerous editorial changes.

Dr. Osburn summarized the sense of the Committee and other reviewers before opening the floor for comment. He stated that the recommendations reached by consensus were to change the title, reorganize the material, add examples and a "road map" and to carefully align the Handbook with the Guidelines and provide cross references.

Dr. Korwek commented that the Committee should carefully consider which material appears in the Guidelines and which appears in the Handbook. He said this was a legal issue. If, for example, specific confinement levels were recommended in the Handbook, these would require public notice and comment.

Dr. Vidaver, Dr. Tolin and Dr. Frey suggested that two separate publications may be needed in lieu of the Handbook--one that contains a general overview and philosophy and one which gives explicit "how-to" direction to researchers.

Dr. Kemp disagreed, saying he believed that if the two parts were separated they would not both reach the intended audience. Dr. Sederoff concurred that researchers need explicit guidance, but he said this would be difficult until the Guidelines were finalized.

Dr. Langston presented APHIS comments on the Handbook, emphasizing the points made in Dr. Gilles' review. She recommended that the Handbook be rewritten stating that the chapter on the National Environmental Policy Act (NEPA) contained misleading inaccuracies and that references to other statutes were also confusing and contradictory. She said that APHIS supports the concept of the Handbook but believes it should be a simple and straightforward manual which would stand alone and not be a supplement to the Guidelines. In order to help redraft the Handbook, she reported that APHIS would be willing to meet with OAB and the editors to present their views in more detail.

Dr. Rissler stated that the issue of which material appears in the Handbook and which appears in the Guidelines is extremely important. She also commented that, as drafted, the Handbook was not merely guidance for researchers, but also an implied policy statement. She stated that the chapter on public relations should be reviewed for tone and content and also cover information on opportunities for the public to interact with USDA on biotechnology issues.

Dr. Young thanked the Committee and guests for their comments. He explained to the Group that the Handbook, once revised, would go to the USDA Committee on Biotechnology in Agriculture (CBA) and back to the ABRAC for approval before being published in the Federal Register for public comment.

Ms. Hollander moved that the Committee give OAB written comments on the second part of the handbook (from page 72 on) and that the Handbook not be released for public comment until after the next ABRAC meeting in January. The motion was seconded.

Dr. Osburn stated that it might be unwise to set a fixed date for publication in the Federal Register because the Committee could make good progress on the Guidelines which would allow for earlier revision of the Handbook. He added that it was important that both the Handbook and the Guidelines be open for public review. Dr. Kemp agreed that OAB and the editors should have the opportunity to go ahead and rework the Handbook after hearing the reviewers' comments and noting progress on the Guidelines.

Ms. Hollander asked to table her motion and to wait and see how much progress was made during the meeting on the Guidelines before deciding how the redrafting of the Handbook should be handled.

USDA GUIDELINES FOR RESEARCH OUTSIDE THE LABORATORY INVOLVING BIOTECHNOLOGY

Dr. Tolin briefly summarized the revised Guidelines section by section. She explained that they were in Federal Register format beginning with the same preamble that had appeared in earlier drafts. She noted that the applicability statement had been omitted because USDA agencies would refer to compliance with the Guidelines in their own instructions to researchers. She also explained that Section II-B "Classification of Organisms" needed to be developed by the Committee, perhaps based on the NIH guidelines. She also noted that the Guidelines stressed that local and state regulations may apply, and that this concept should be developed in the Handbook. She stated that Section IV had been reworked by the Working Group so that it now varied from the Handbook. For example, the Guidelines no longer required each institution to have a biosafety officer. This officer is required by NIH and is concerned primarily with human pathogens. Finally, in Section VII, the definitions had been moved to the end and separated from other materials.

Dr. Vidaver expressed support for the draft Guidelines as a whole because they are process independent and based on risk of the modified organism relative to the risk of the parent organism. She added, however, that it is not readily apparent how all the parts of the Guidelines fit together. She stated the section on Classification of Experiments was a departure from other documents, but was somewhat analogous to the NIH appendix on working with modified plants and microorganisms in greenhouses.

Dr. Korwek stated that he generally supported the approach taken by the Guidelines, but that many specifics were missing. He stated that one of the issues which remained to be resolved was consistency between confinement levels and types of experiments. He also said that the language in the document lacked legal precision. For example, the term "no risk" should be replaced by "risk of no consequence." He also pointed out that the level and the nature of risk are both components of total risk. He stated that the Committee needed to decide which material should be in the Guidelines and which should be in the Handbook. He concluded that the Guidelines were a good first step, but that the Committee needed more time to give them thorough consideration.

Format and Structure

Dr. Osburn called for comments on the way in which the Guidelines document is put together (format, order, and sequence).

Dr. Korwek advocated addition of an applicability section including a description of how defunding penalties will work for non-compliance in

the first section of the Guidelines. Other Committee members agreed that it was important to make compliance clear from the outset.

Dr. Tolin and Dr. Young explained that the applicability section had been taken out because USDA research funding agencies will include this information in their grant application and award materials. This approach had been recommended to OAB by the Office of the General Counsel (OGC) of USDA.

Dr. Kemp asked if noncompliance with the Guidelines would result in the cutoff of all USDA funding to the institutuion or only funding for the project in question. Dr. MacKenzie replied that this issue is still unclear and that OAB should do some research to determine how this issue was being handled by other agencies.

Dr. Vidaver suggested that the applicability section include wording such as "These Guidelines apply to all USDA funded research. As with NIH, voluntary compliance by other researchers is encouraged." Dr. Osburn suggested OAB draft an applicability statement drawing on the suggested wording by Dr. Vidaver.

Dr. Tolin moved that the Committee adopt the general format presented for the Guidelines, with the addition of an applicability statement. The motion was seconded. It was passed unanimously.

Philosophy of the Guidelines

Dr. Osburn called for comments and discussion on the general philosophy of the Guidelines.

Dr. Frey asked what is the legal context of the Guidelines? He also inquired whether a broad versus narrow definition of "biotechnology" would have implications if the Guidelines were challenged in court?

Ms. Hollander answered that the Guidelines could be challenged under NEPA either as too narrow or too broad, but she believed a narrow definition was more likely to lead to litigation. Dr. Korwek concurred, saying it was difficult to predict what legal actions might be taken. However he advised the Committee to base the Guidelines on sound scientific knowledge which is the best way to defend decisions.

Dr. Young responded that OAB had been advised to put together an environmental assessment (EA) for the Guidelines. Dr. Osburn added that the process of public review will help in developing a document which is legally and scientifically defensible.

Dr. Sorensen asked if NIH had ever considered widening their scope beyond recombinant DNA? Dr. Vidaver responded that NIH had considered widening their purview, but had decided that other technologies did not yet merit such close attention.

Dr. Hafs moved that the Committee accept the general philosophy of the Guidelines--that they are process independent, based on biological principles and give guidance to researchers. The motion was seconded. Dr. Osburn called for discussion on the motion.

Dr. Sederoff expressed hope that if the Committee accepted the broad definition of biotechnology, it would also be able to exempt most of classical plant breeding.

Dr. Frey asked if such exemptions would require an EA supporting each choice? Dr. Parry advised that, in his opinion, it would be better to keep the definition of biotechnology narrower, because although exemptions can be made, they would have to be considered on a case by case basis. Dr. Parry added that the Agricultural Research Service (ARS) had already prepared EA's for some areas of classical agricultural research such as the germplasm program, and that the courts have ruled that the program, as a whole, does not have a significant impact on the environment.

Dr. Purchase stated that since the Guidelines were using processes (types of experiments) to set up the confinement levels, he did not believe the Guidelines were completely "process independent". Dr. Sederoff and Dr. Tolin explained that although processes are mentioned, they are coupled with organisms as a tool for determining risk and thus the thrust of the Guidelines is on product. Dr. MacKenzie added that the process versus product issue has been misunderstood. At the time of the Federal Coordinated Framework, the consensus was that regulatory agencies should only regulate products and not oversee the research process in laboratories. He expressed the view that since the Guidelines are not regulations they can use process to help determine risk.

Ms. Hollander added that at the time NIH set up the Recombinant DNA Advisory Committee (RAC), recombinant DNA was thought by some to present a high risk. Subsequent experiments, monitoring, and evaluation led most scientists to conclude that this assumption was false. She added that this experience had led the scientific community to acknowledge that a given process is not a priori high risk by itself, but, this does not mean that process cannot be one component of risk assessment.

Ms. Hollander called for the question on Dr. Hafs' motion that the Committee approve the philosophy of the Guidelines. The motion was passed, six in favor, five against, and one abstention. Because of the close vote, Dr. Young suggested the issue be reconsidered later in the meeting. Dr. Osburn suggested that the Committee move ahead and consider the Guidelines section by section and then revisit the question of philosophy later in the meeting.

Dr. Korwek suggested that the main problem in development of Guidelines may rest with the broad definition of "biotechnology," which he doubted had utility, but he believed the Committee should move ahead and then change the definition later if necessary. Ms. Hollander moved that for the purposes of discussion the Committee accept the broad definition of biotechnology as presented by the Working Group on Definitions with the understanding that it could be changed later by the ABRAC if necessary. The motion was seconded and passed, eleven in favor and one against.

I. Purpose of the Guidelines

Dr. Osburn called for comments and discussion on Section I of the Guidelines.

Dr. Frey suggested that the phrase "when the products are not regulated by other Federal agencies", be added which would exclude products overseen by APHIS and EPA. Ms. Hollander concurred that regulations should be preeminent where applicable. Dr. Osburn asked for a straw vote on the request that a statement clarifying that regulatory authority supercedes the Guidelines be added. This was passed, eleven for, and 1 against.

II. Classification of Experiments

Dr. Tolin reiterated that this section contained several components of the Guidelines which would need to be integrated into Section III, "Conduct and Review of Experiments." She then recommended several changes in wording to the Committee.

Dr. Vidaver and Dr. Tolin explained that subsection II-A-1-e would contain a list of organisms for which there was a long history of safe use and which were generally recognized as compatible with the environment (GRACE). This list would include most crops and domestic animals.

Dr. Gorham said that differentiating between types of organisms was extremely important. For example, dangerous pathogens such as foot and mouth disease would require stringent confinement regardless of the modification made.

Dr. Purchase asked if the type of modification would affect the recommended level of confinement. Dr. Tolin and Dr. Sederoff replied that it would be one of the factors of risk considered, but that the weight given to type of modification relative to other factors in deciding on confinement levels had not yet been decided. Dr. Purchase disagreed with this approach, stating that the type of modification did not represent a continuum of risk. Dr. Korwek agreed with Dr. Purchase, but said he believed that the approach taken in the Guidelines should be fully developed before a final decision could be reached by the Committee on this issue.

Dr. Frobish asked the Committee how low, moderate and high risk would be defined? Dr. Sederoff answered that examples would be given of each. Dr. Whitmore and Ms. Hollander noted that based solely on the descriptions given in the Guidelines, it was difficult to distinguish between levels of risk. Dr. Tolin and Dr. Gould concurred that the Guidelines should give examples of each category listed.

Ms. Hollander and Dr. Whitmore stated that three categories (low, medium and high) would be preferable to the four categories of risk in the Guidelines. Dr. Tolin explained that the first three categories covered three known types of modifications and that the fourth category covered all new types where the level of risk is uncertain.

Dr. Gould suggested that the Guidelines be drafted without using negative language such as "not included in Type 1 or Type 2" and instead use positive, descriptive language and give concrete examples. He also recommended the Guidelines clarify that category 4 referred to uncertainty rather than high risk. He also stated that the question of scale is very important. Although a change might rarely occur through natural mutation, biotechnology greatly increases the scale of the release into the environment of the modified organism. Dr. Purchase added that occasionally natural mutations occur which cause an organism to become very virulent.

Dr. Tolin handed out a draft of Section II-B, "Classification of Organisms." She explained that the characteristics of Status 1, i.e., GRACE, organisms were taken from the Office of Technology Assessment (OTA) report; i.e., organisms with a long history of use with no or low potential for negative effects on the environment, including low potential for: (a) reproduction in the environment, (b) transfer of genetic information to other species, and (c) rapid dissemination in the environment. GRACE organisms for all practical purposes are not known to be plant pests or pathogens. She stated that the Committee would need to draw up a list of Status 1 (GRACE) organisms.

Dr. Bothast inquired if the list would be all inclusive or just give examples. Dr. Tolin replied it would be a list of all the organisms the Committee decided fit the category, and that it could be changed by decision of the Committee or through another administrative mechanism which the Committee set up.

Dr. Tolin presented the requirements for Status 2 organisms, i.e., those which had some potential for the negative effects on the environment according to the OTA criteria. They also may have no history of domestication or be a pest or pathogen of predictable low consequence in the environment.

Dr. Tolin then presented the criteria for Status 3 organisms, which would have two or more of the traits a-c; and Status 4 organisms, which have two or more of the traits a-c listed above and are known to be a pest or pathogen of high consequence in the environment.

Dr. Tolin noted that genetic modifications might change an organism from one status to another or a modification might be status neutral. For example, classical breeding of most crops would not effect their status as GRACE organisms, however, if a genetic modification increased the virulence of a pathogen it would result in the organism being moved up a category from Status 2 to Status 3, or from Status 3 to Status 4. In conclusion, Dr. Tolin explained that levels of recommended confinement would be based on the classification of the organism after the modification was taken into consideration. Thus, confinement levels were based on a matrix of considerations.

Dr. Korwek inquired how the matrix would work in practice. Dr. Sederoff replied it would involve a three step process, starting with the non-modified organism which would be assigned a particular status. The second step would be to assess the impact of the modification on the status of the organism. The third step would be to determine appropriate confinement of one or more types (physical, biological, etc.). Dr. Tolin added that real case studies could be put through this process to see if the results were adequate, and that, in theory, it was possible for an organism to be moved into a lower status category through modification.

Dr. Kemp expressed support for the approach, but he was concerned that the Principal Investigator (PI) would have to go through complicated processes, even for standard experiments involving Status 1 organisms. Dr. Sederoff said that level one (or perhaps level zero) experiments could be exempted.

Dr. Gould pointed out that the different types of confinement are not necessarily additive to create increased stringency, but they may interact synergistically.

Dr. Raleigh stated that it was important for the Guidelines to refer explicitly to EPA and other regulations and to point out to researchers that these still must be followed. Dr. Wodzinski added that the Guidelines might include a list of which regulatory agencies are responsible for which types of organisms. Dr. Langston agreed, noting some organisms will always be regulated, and the Guidelines should not confuse the issue.

Dr. Serdy requested that the Committee reconsider its basic charge. He stated that in his view, the public considered "biotechnology" to mean recombinant DNA and that to describe "biotechnology" as any change in nature was a disservice to the public. He recommended that the

Committee change the definition of "biotechnology" and narrow the focus of its discussions. Dr. Sederoff replied that the Committee had dealt with this issue repeatedly and continued to be confronted with a basic, logical inconsistency. Recombinant DNA is a process which possesses no added hazard, therefore, there should be no reason to regulate it. He did, however, recognize, that by accepting a broader definition of "biotechnology" the Committee needed to develop guidelines which exempted certain kinds of research.

In order to provide an opportunity for review of the Guidelines in more depth, Dr. Osburn suggested that the Committee break into three discussion groups as follows:

Classification of Experiments - Dr. Whitmore (Chair), Dr. Tolin, Dr. Korwek, Dr. Frey, Dr. Langston, and Dr. O'Berry.

Confinement - Dr. Kemp (Chair), Dr. Gorham, Dr. Sorensen, Ms. Hollander, Dr. Parry, Dr. Purchase, Dr. Jones.

Classification of Organisms - Dr. Bothast (Chair), Dr. Vidaver, Dr. MacKenzie, Dr. Hafs, Dr. Gould, Dr. Sederoff, Mr. Stern.

Dr. Osburn stated that the charge to all three discussion groups was to go back over the pertinent sections of the Guidelines and to make changes where appropriate. He said the discussion groups should also review the levels of responsibilities for the PI, IBC, ABRAC, and USDA described in the Guidelines.

The minutes of the three discussion groups are attached as Appendices C, D, and E, respectively. After the full Committee reconvened, Dr. Osburn asked for reports from the Chairperson of each discussion group.

Classification of Experiments

Dr. Whitmore said the group had reached no definite conclusions. Some members of the group approved of the general approach taken in the Guidelines, while others believed the whole approach taken involving the classification of experiments was incorrect. Dr. Whitmore stated that the group believed that this impasse might be a result of problems with the broad definition of "biotechnology" tentatively accepted by the Committee. Therefore, the group had taken another look at this definition. The general consensus of the group was that the definition should be narrowed to take out reference to classical techniques. If this were done, it might not be necessary to include a classification of experiments in the Guidelines. This would leave the status of the organism and the effect of the experiment on this status as the central factors in determining the level of confinement.

Classification of Organisms

Dr. Bothast reported that the group had worked on Section II-B as presented to the Committee. The group had discussed the meaning of "uncontrollable reproduction" and had added several phrases to clarify the meaning of "domestication." They also recommended that lists of organisms in each status be developed as an appendix. These lists would be flexible and open to public review. The group believed that such a list would be very helpful to researchers in understanding the Guidelines. He also reported that the group had restructured the wording of the characteristics and explicitly added biocontrol organisms to Status 1. The group had also recommended amending Status 3 organisms to include pests or pathogens of moderate consequence, and changing Status 4 to include organisms which exhibited one or more (rather than two or more) of the characteristics listed in Status 1. The group also gave examples for each status as follows:

Status 1	Corn
	Cattle
	Rhizobium
Status 2	Laboratory mice
	Sorghum
	Oats
Status 3	Corn leaf blight
	Kudzu
	Water hyacinth
Status 4	Corn lethal necrosis
	Foot and mouth disease
	Gypsy moth
	Striga

Confinement

Dr. Kemp reported that the group agreed that it was extremely important to define level one confinement as minimal for organisms which are of minimal or no consequence to the environment, so as to make it clear that standard agricultural research could be continued to be conducted as it had in the past. Ms. Hollander suggested that Level 1 consist of standard good agricultural practices (GAP).

Dr. Purchase said that the group had discussed several alternate approaches to the issue of confinement but had concluded that the five levels proposed were the best way to describe what really is a continuum between GAP and maximum confinement. The five levels of confinement would be successively more stringent. Ultimately, however, it would be necessary to use judgment to determine what category of confinement (physical, biological, etc.) or combination of categories was appropriate for a given organism.

Dr. Gorham and Dr. Kemp stated that if "biotechnology" is not redefined, there should be a "0" level of confinement added.

Dr. Vidaver suggested that "agricultural practices" should also include forestry and mariculture.

Definition of Biotechnology

Dr. Osburn thanked the discussion groups for their efforts. He stated, that the whole issue seems to be how to fit things into categories in a manner which does not impede research and development and yet ensures that adequate measures are taken for those efforts which really do constitute a risk. He also stated that the broad definition of "biotechnology" was making this process difficult and thus suggested that the discussion on the definition be reopened.

Dr. Hafs moved that the Committee reconsider the definition of biotechnology. The motion was seconded. Dr. Osburn called for discussion.

Ms. Hollander stated that it would be unwise to change the definition of biotechnology until further work is done on the Guidelines. Dr. Sederoff agreed, noting that if the definition is changed, then the Guidelines would have to be changed. Dr. Kemp and Dr. Vidaver stated they would like to see the discussion reopened in light of the discussions during the Committee meeting. The motion to reconsider the definition of biotechnology was put to a vote and passed, nine in favor, one opposed, and no abstentions.

Dr. Osburn reopened discussion of the definition of biotechnology. The following definition had been distributed previously to the Committee by the OAB staff for consideration: "Biotechnology: The process of causing genetic variation in living organisms through the introduction of foreign DNA or RNA. This includes but is not limited to: recombinant DNA and genetic manipulations involving RNA between species accomplished with or without specific molecular gene vectors; using physical methods such as electroporation, microinjection and microprojectile procedures; cross species cell and embryo fusion techniques; and directed mutagenesis. Biotechnology, for purposes of these guidelines, does not include methods to study or to use genetic variation that occurs in nature or that results from artificial breeding methods such as hand pollination, artificial insemination, superovulation, embryo transfer, selection of somaclonal variants, or introduction solely of same-species DNA or RNA."

Ms. Hollander stated she favored retaining the broad definition, [i.e., the application of biological systems and organisms to technical and industrial processes] stating that other Federal agencies use the broad definition. She stated that she doubted USDA would run into any problems under NEPA by exempting classical plant breeding and other standard agricultural research in the Guidelines. Furthermore, she believed the broad definition to be scientifically correct. She suggested, however, that the Committee might wish to define "genetic

engineering" which would be considerably narrower, and quite similar to the definition distributed by OAB.

Dr. Tolin stated she preferred the following definition used by OTA:

> "Biotechnology is broadly defined to include any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop micro-organisms for specific use. This report focuses on 'new biotechnology' (e.g., recombinant DNA techniques, cell fusion, and novel bio-processing techniques) rather than 'old biotechnology' (e.g., use of micro-organisms for brewing and baking or selective breeding in agriculture and animal husbandry)." [from U.S. Congress, Office of Technology Assessment, New Developments in Biotechnology: U.S. Investment in Biotechnology - Special Report OTA-BA-360 (Washington, DC:U.S. Government Printing Office, July 1988).]

Dr. Frey and Dr. Tolin agreed with Ms. Hollander that the definition distributed by OAB should be for "genetic engineering" rather than biotechnology. Dr. Vidaver disagreed, stating that "genetic engineering" normally referred only to recombinant DNA.

Dr. Kemp stated that he favored the definition distributed by OAB because it was not process oriented and included all transfers of genes from outside the species. Dr. Gorham and Dr. Osburn agreed, stating they favored the OAB definition because the definition would eliminate conventional embryo transfer technology.

Dr. Purchase commented that microinjection was still covered by the OAB definition. Dr. Kemp agreed, except for microinjection of genetic material from the same species.

Dr. Tolin stated she was not in favor of the definition distributed by OAB because it described techniques and was not consistent with the definitions used by other agencies. She also stated that the source of DNA (same versus a different species) is not a good criterion for risk.

Dr. Frey moved that the Committee accept the definition proposed by OAB as a working definition in order to narrow the scope of the Guidelines, with the understanding that it could be redefined again, later, if necessary. The motion was seconded. Dr. Osburn called for discussion.

Dr. Tolin and Ms. Hollander stated that the Committee had not given the new definition enough consideration and that there were not sufficient reasons to redefine "biotechnology" at this time.

Dr. Tolin moved to table the motion. The motion was seconded. It was defeated, three in favor, six opposed, and one abstention.

Dr. Osburn called for a vote on the original motion of Dr. Frey. It was passed, six in favor, three opposed, and one abstention.

Charge to OAB on Redrafting the Guidelines
Dr. Osburn asked OAB to take into consideration the recommendations of the various discussion Working Groups and redraft the Guidelines for resubmission to the ABRAC.

Dr. Young requested that OAB also be authorized to call another Working Group meeting if this was necessary to assist in redrafting the document.

"Roles and Responsibilities"
Dr. Osburn called for general comments on Section IV of the Guidelines. Because of time constraints, he asked that members leave specific comments with OAB.

Dr. Frey and Dr. Tolin asked about the subsection on public disclosure. They expressed concern that it might allow some pre-patent information that was not explicitly marked "Confidential Business Information" to be made public. Dr. Young replied that this section was taken from the NIH guidelines.

Ms. Hollander asked if the Committee believed 30 days was too long a period to give institutions to report problems related to biosafety? Dr. Serdy stated he thought 15 days would be sufficient. Ms. Hollander replied the Guidelines should state "no longer than 15 days and as soon as possible." Dr. MacKenzie explained that there were two types of notification, an immediate telephone call and formal written notification which could take up to 15 days. Dr. Young said OAB would rework this section in consideration of the Committee's suggestions.

Responsibilities of the Institutions
Dr. Frey brought up the conflict of interest requirements regarding IBCs. He stated that the phrase "be involved with" was a bit vague and that in small institutions almost every scientist was "involved with" the work of colleagues.

Ms. Hollander stated that she believed the Guidelines should prohibit colleagues from reviewing each other's experiments on IBCs. Dr. Tolin and Dr. Frey disagreed, saying small institutions couldn't function if this were prohibited. Dr. Sederoff and Dr. Frey suggested that the Guidelines differentiate between those who actively collaborate or who have an adviser/student relationship and colleagues who are simply knowledgeable about each others' work. Dr. Sederoff suggested that active collaborating scientists be barred from reviewing each others' proposals for at least five years.

Dr. Kemp asked if the section of the Guidelines dealing with IBCs was consistent with the NIH guidelines? He stated that consistency was important otherwise it would be burdensome to institutions to operate two similar committees with different rules. Mr. Stern replied that the NIH guidelines set up separate standards for IBCs for public research institutions and IBCs for other research organizations. He said the NIH requirements had been synthesized to create the section on IBCs in the USDA Guidelines. Ms. Hollander commented that the new EPA regulations would require Environmental Biosafety Committees (EBC's) and that the ABRAC may wish to coordinate with EPA before proceeding. Dr. Young responded that OAB has been in contact with EPA on this issue.

Dr. Tolin asked the Committee to consider the wording of the phrase requiring IBC members to have "the capability to assess safety of research and experimentation with reference to health and the environment." She asked if the phrase should instead say, "public health". Dr. Osburn stated it should be as broad as possible and include animal as well as human health.

Responsibilities of the Principal Investigator
Dr. Purchase noted that the responsibilities of the PI listed in the Guidelines and the Handbook should be made more consistent. Ms. Hollander commented that the responsibilities assigned to the PI in the Handbook were unrealistically broad, and that some of these responsibilities should be assigned to the institution. Dr. Serdy added that the Handbook required both PI's and institutions to report problems to USDA, and that this was duplicative. Dr. Kemp commented that it should be the institution's responsibility to report problems, since the contract for research was between USDA and the institution and not between USDA and the PI. He recommended that responsibility for reporting problems be given to the IBC. Dr. Langston commented that the regulatory requirements were for the PI to build in a monitoring system and emergency procedures into the design of the experiment, and that this requirement should be mentioned in the Handbook or Guidelines when discussing development of protocols.

Responsibilities of the ABRAC and OAB
The Committee expressed no comments on these sections.

Protection of Proprietary Data
Dr. Frey stated that this section was too general. He said the Guidelines should give more specific assurances that proprietary data would be protected. Dr. Vidaver suggested OAB check the NIH guidelines on this issue. Ms. Hollander suggested the Guidelines or Handbook might give guidance to the public on how to obtain information which is not proprietary.

Amendments

Dr. Langston recommended that this section be expanded to require that petitions submitted to OAB contain a justification for the change advocated which would allow the request to be evaluated scientifically. Dr. Vidaver added that requests for changes would have to be open for public comment. Dr. Young replied that proposed changes would be published in the Federal Register.

Definitions

Dr. Osburn asked if the Working Group on Definitions needed to meet again to develop further definitions? Ms. Hollander replied, that in her opinion, it was unnecessary, and that OAB could develop the additional definitions needed. Dr. Osburn asked the Guidelines Working Group to report to OAB what additional definitions were needed, such as "biocontrol" and "stringency."

Philosophy of the Guidelines

Dr. Osburn asked the Committee if it wished to reconsider adopting the philosophy of the Guidelines. Dr. Tolin moved that this discussion be tabled until the next ABRAC meeting. The motion was seconded, and passed, ten in favor, none opposed, and no abstentions.

Dr. Osburn asked the Committee to send written comments on the Handbook to OAB. He thanked the Committee for their participation, and for their contributions to the progress made on the Handbook and the Guidelines. Dr. Osburn then adjourned the meeting.

Martha Steinbock

MARTHA STEINBOCK
Rapporteur

Alvin R Young

ALVIN YOUNG
Executive Secretary

Bennie V Osburn

BENNIE OSBURN
Chair, ABRAC

APPENDICES

MEMBERS

UNITED STATES DEPARTMENT OF AGRICULTURE

AGRICULTURE BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE

September 22-23, 1988

Bennie I. Osburn, D.V.M., Ph.D. (Chair)
Department of Veterinary
Pathology
School of Veterinary Medicine
University of California, Davis
Davis, CA 95616
(916) 752-6865 & 7746

Harold D. Hafs, Ph.D.
Animal Science Research and
Development
Merck, Sharp & Dohme Research
Laboratories
Rahway, NJ 07065
(201) 750-8359

John R. Gorham, D.V.M., Ph.D.
Animal Disease Research Unit
Agricultural Research Service
Washington State University
Pullman, WA 99164-7030
(509) 335-6029

A. Ann Sorensen, Ph.D.
Natural & Environmental Resources
American Farm Bureau Federation
225 Touhy Avenue
Park Ridge, IL 60068
(312) 399-5784

Fred Gould, Ph.D.
P.O. Box 7634
Department of Entomology
North Carolina State University
Raleigh, NC 27695-7634
(919) 737-2638

Frank W. Whitmore, Ph.D.
Division of Forestry
Ohio Agricultural Research and
Development Center
Ohio State University
Wooster, OH 44691
(216) 263-3783

Nicholas M. Frey, Ph.D.
Director, Technology Acquisition
and Development
Pioneer Hi-Bred International
700 Capital Square
400 Locust Street
Des Moines, IA 50309
(515) 245-3643

John D. Kemp, Ph.D.
Director, Plant Genetic Engineering
Department of Plant Pathology
New Mexico State University
Las Cruces, NM 88003
(505) 646-5453

Sue A. Tolin, Ph.D.
Department of Plant Pathology,
Physiology, and Weed Science
Virginia Polytechnic Institute
and State University
Blacksburg, VA 24061
(703) 961-5800

Rodney Bothast, Ph.D.
USDA Agricultural Research Service
Northern Regional Research Laboratory
Peoria, IL 61604
(309) 685-4011

Edward Korwek, J.D., Ph.D.
Hogan and Hartson
555 13th Street N.W.
Washington, D.C. 20006
(202) 637-5661

Anne K. Hollander, M.A.
Associate
The Conservation Foundation
1255 23rd Street N.W.
Washington, D.C. 20037
(202) 293-4800

Linda Phaire-Washington, Ph.D.*
Department of Biology
Carver Research Foundation
Tuskegee University
Tuskegee, AL 36088
(205) 727-8125

Alvin L. Young, Ph.D. (Executive Secretary)
Director
Office of Agricultural Biotechnology
U.S. Department of Agriculture
14th and Independence Avenue S.W.
Washington, D.C. 20250
(202) 447-9165

* Unable to attend

AUTHORITIES, RESPONSIBILITIES AND OBLIGATIONS FOR BIOSAFETY (page numbers)

ORGANIZATIONAL LEVEL	REGULATION OF ARTICLES AND PRODUCTS	REVIEW OF RESEARCH PROCESS	PUBLIC UNDERSTANDING AND ACCEPTANCE
rincipal Investigator	Permit Application (19)	Project Proposal (80, 97)	Impact of Socio-economic (45) and Ethics (57)
nstitution		IBC Review and Biosafety Officer (72)	Public Relations (14)
overnment	Permissions and Licenses (19, 36)	Scientific Committees Advisory to Administrative Authority (12, 36, 87)	Compliance (36)

Appendix E

DRAFT

U.S. DEPARTMENT OF AGRICULTURE

AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE DISCUSSION GROUP ON CLASSIFICATION OF EXPERIMENTS

Minutes of Meeting, September 23, 1988

The Agricultural Biotechnology Research Advisory Committee (ABRAC) ad hoc Discussion Group on Classification of Experiments convened on September 23, 1988 with Dr. Frank W. Whitmore as the Chair. Members of the Discussion Group included Edward Korwek, Nicholas Frey, Sue Tolin, Althaea Langston and Phillip O'Berry.

Members suggested that the order of the guidelines be changed by placing Section II-B on classification of organisms before classification or types of modifications. Dr. Frey expressed concern about the term "risk." He observed that there were no criteria for setting risk levels since the levels had not been define, and he suggested that the terminology of risk be deleted. Dr. Whitmore asked if the introductory statements could be deleted and if the classification (types) are sufficient to take care of status changes. Members expressed the view that risk should not be related to the way an organism is modified.

Dr. Langston suggested removing the first four lines of the introductory paragraph under Section II. Dr. Tolin stated that this could be rewritten after the classifications had been completed. Dr. Langston suggested revising the outline and rewriting the section in the guidelines to fit the outline. She suggested inclusion of a

classification of experiments, a description of modifications, and a section on potential public concerns.

Dr. Korwek observed that it is probably not possible to classify experimental techniques. He stated that the status concept appealed to him, but he saw a problem in dealing with modifications in context with the status of assigning levels. He said he could not see how the nature of the modification entered into assigning levels.

Members suggested that the definition of "biotechnology" should be narrowed down from the broad definition developed previously by the Definitions Working Group.

Dr. Tolin suggested that the statements on standard breeding practices and somaclonal variation (Section II-A-1-a) and fusion of cells and embryos (Section II-A-1-b) be deleted thus leaving three subcategories.

Dr. Whitmore suggested the addition of a statement in the guidelines that would put the burden of proof regarding the type of modification on the principal investigator (PI). The Discussion Group agreed to eliminate the ranking of techniques.

Eva Russnak
Rapporteur

U.S. Department of Agriculture
Agricultural Biotechnology Research Advisory Committee
Minutes of the Confinement Discussion Group Meeting

September 23, 1988

The Confinement Discussion Group Meeting, Chaired by Dr. John Kemp, consisted of the following members: Ms. A. Hollander and Drs. J. Gorham, A. Sorensen, G. Purchase, R. Parry, and D. Jones. The charge issued to the group was to assign or define confinement levels in light of the classification scheme developed by Dr. Tolin. The Discussion Group met during the ABRAC Meeting of September 23, 1988.

Dr. Kemp noted that the guidelines and the handbook were inconsistent in their discussions of confinement. Dr. Purchase replied that the principles of confinement must be decided first; the handbook would be made to match those decisions later.

Dr. Sorensen suggested that confinement principles may vary for each organism. For example, special confinement for some engineered variations in corn may not need to be considered. Dr. Kemp asked whether containment principles would imply regulations for all biology, i.e., all farming or plantings. Dr. Purchase suggested that the lowest confinement level would be considered normal farming practices and that no review would be required. Categories of reviewed experiments and stringency levels are necessary to define containment levels.

A discussion of using farming practices as a device for specifying a level of confinement requiring no review followed.

Dr. Kemp asked if good farming practices or confinement principles would have to be listed. Ms. Hollander suggested that level 1 could be considered good farming practices. Dr. Kemp questioned whether good farming practices could be defined. Dr. Purchase noted that good farming practices vary by organism and by location, making any such definition impossibly long. Dr. Parry said that good farming practices would be difficult to prescribe. He suggested that the PI or IBC could define conditions based on his/her own knowledge. However, that knowledge was unlikely to include any information about behavior of the engineered organism outside the lab, i.e. in a mixed species environment.

Ms. Hollander asked what constitutes low, medium, and high confinement levels. A discussion about confinement elements absent from level 1 containment followed. The discussion group consensus appeared to favor a substitution of "good farming practices" for "standard farming practices," making this description compatible with "good agricultural practices" terminology often used by international organizations. Section II-C-4-a was changed to read as follows:

Confinement Level 1. Level 1 consists of good agricultural practices appropriate to the experimental organism and test site. This includes instructions for all personnel on appropriate record-keeping. It also includes planting, inoculating, reproduction, husbandry, harvesting, slaughter, and disposal practices that would be used on a well managed farm. Good agricultural practices are appropriate when there are no unreasonable adverse effects associated with the test organisms and their products.

The use of the term "risk" was agreed to mean unreasonable adverse effects to health and environment.

Dr. Parry asked how to define containment and whether general containment principles would mean an attempt to prevent exit or exit and entrance. Dr. Gorham noted that the nature of the organism dictates appropriate barriers, e.g. deer require a 10' fence while tick research may require an entirely different barrier.

Ms. Hollander suggested defining the various containment levels as similar physical barriers, but with differing levels of monitoring and contingencies.

Dr. Kemp asked whether examples should be used in the guidelines to detail appropriate containment levels. It was noted that there are many different confinement methods (physical barriers, biological containment, etc.) and many different animal species for which appropriate containment methods would differ. Hence, examples would be too numerous to be profitably included. Instead, it was suggested that researchers should be told to use whatever means possible to achieve the appropriate level of confidence that escape will not occur. Appropriate levels will be decided later. The probabilistic notion could serve as a fallback definition of "stringency."

Dr. Kemp suggested that confinement levels more stringent than level 1 could be constructed by adding confinement requirements. Level two could be defined by the addition of one extra confinement technique. Level three could be defined by the addition of two extra confinement techniques. Level four would

require as many confinement techniques as appropriate, depending on the organism.

Dr. Parry initiated a discussion on the principles intended in confinement. Instead of discussing 5 methods of confining an organism, one could discuss limiting reproduction and dispersal. Persistence must also be considered.

The discussion group determined that the following information could serve as a preamble to the confinement discussion:

Greater confinement than is provided by these basis practices can be obtained by employing (a) practices of more than one category simultaneously and/or (b) practices of greater stringency (significantly higher level of confidence that the organism is confined). There is a continuous progression in degree of confinement for organisms tested in the environment from good farming practices (Level 1) to maximum confinement (Level 4).

Fred Kuchler
Rapporteur

Appendix E

U. S. DEPARTMENT OF AGRICULTURE
AGRICULTURAL BIOTECHNOLOGY RESEARCH ADVISORY COMMITTEE
MINUTES OF THE WORKING GROUP MEETING ON CLASSIFICATION OF ORGANISMS
September 23, 1988

Dr. Rodney Bothast, chair, convened the Working Group on Classification of Organisms (henceforth referred to as the Working Group) during the second day of the United States Department of Agriculture (USDA) Agricultural Biotechnology Research Advisory Committee (ABRAC) meeting of September 23-24, 1988.

Members present included:
Rodney Bothast (Chair), USDA, Agricultural Research Service
Fred Gould, North Carolina State University
Anne Vidaver, University of Nebraska
Ronald Sederoff, North Carolina State University
Harold Hafs, Merck, Sharp & Dohme Research Laboratories
David MacKenzie, USDA, Office of Agricultural Biotechnology
Paul Stern, University of Florida
Judith Weiss (Guest), National Association of Biological Sciences

Dr. Bothast opened the meeting by inquiring if the Working Group wanted to discuss the wording of the handout of Section II-B "Classification of Organisms" of the USDA Guidelines for Research Outside the Laboratory Involving Biotechnology (henceforth referred to as the Guidelines) or alternatively if the Working Group preferred to deal only with concepts. The consensus was that the Working Group would work on key phrases which were based on concepts and leave the editing of Section II-B to the Office of Agricultural Biotechnology (OAB). The Group reached consensus that it will be useful to give examples of each type of organism because this would be of practical value to the researcher. The draft Section II-B as handed out to the ABRAC appears as Appendix I to these Minutes.

Dr. Gould opened the discussion of Subsection II-B-1 "Status 1 Organisms." He stated that criteria "c," "uncontrollable reproduction" and criteria "b," "rapid and widespread dissemination in the environment" were confusing. In his opinion, these categories overlapped because reproduction is normally how organisms spread. He also stated that few, if any, microorganisms would have low potential for "b" and "c" as currently written. Dr. Vidaver disagreed stating that although microorganisms are only really useful if they can reproduce and at least maintain themselves in the environment, there are microorganisms for which reproduction could be controlled.

Dr. Bothast expressed concern that Section II-B might be too long if the ABRAC tried to list organisms in each catagory. Dr. Vidaver stated that the lists would not be exhaustive and that organisms could be added, deleted or moved by the ABRAC as desired. Dr. Hafs suggested that the ABRAC could begin by using the National Institutes of Health (NIH), Center for Communicable Diseases (CDC) and the Environmental Protection Agency (EPA) lists as a place to start. The Working Group agreed to this by consensus, however, Dr. Vidaver stated that the NIH, CDC, and EPA lists would not contain some organisms commonly used in agricultural biotechnology research. The OAB has agreed to obtain these lists. The NIH list is attached as Appendix III. The EPA list has been requested but has

not yet been received.

Dr. Hafs suggested that the Working Group add the words "such as" and give examples of each type of organism. The Working Group reached consensus that this would be a good idea and of practical value to the researcher.

Dr. Gould stated that it was unclear if the lists of organisms would refer to species as a whole, or genera, or perhaps strains of species. Drs. Sederoff and Hafs replied that the list should refer to species since the Working Group on Definitions had stated in the definition for "organism" that an organism must be self perpetuating.

Dr. Sederoff, referring to Section II-B-1, asked about including biocontrol agents which were pests or pathogens but were beneficial. Dr. Vidaver suggested that the criteria for Type I organisms be amended as Type I organisms so biocontrol organisms would qualify. Dr. MacKenzie suggested that the last phrase of Section II-B-1 be drafted to read "and is not a pest or pathogen (except for biocontrol agents)." The Working Group agreed to forward this suggestion to the ABRAC. A draft of Section-II-B which contains this and other recommendations of the Working Group appears as Appendix II.

Dr. MacKenzie stated that he had trouble differentiating Type 3 organisms from Type 4 organisms. Dr. Hafs suggested the language in Type 4, be amended to read, "an organism with one or more of the above traits.." rather than "with two or more of the above traits." He also recommended that the phrase "and is not a pest or pathogen" be added to Section II-B-3 describing Type 3 organisms. Dr. Bothast suggested this might not be consistent with the other Types and suggested instead, "and is a pest or pathogen with generally moderate consequence in the environment." The Working Group reached consensus to recommend this change to the ABRAC.

Dr. Weiss pointed out that the formatting of Section II-B-1 was incorrect, and therefore the clauses "and has a history of domestication and has non-pest or pathogen status" seemed to refer to "uncontrollable reproduction" rather than all Status 1 organisms. The Group agreed these clauses should be moved to the introductory sentence of the Status 1 description.

Dr. Gould said he did not like the phrase "history of domestication" in Section II-B-1. He said it was not scientific and was confusing. Dr. Sederoff disagreed, saying he liked the word because it was a familiar word with benefical psychological connotations. Dr. Sederoff added that "domestication" was a scientific process based on repeating experiments many times over thousands of years. Dr. Bothast suggested the phrase "for which there is an extensive biological knowledge (e.g. domesticated organisms or organisms with a long history of use)" be substituted for "has a long history of domestication." The Working Group agreed to suggest this change to the ABRAC.

Dr. Bothast, at the request of ABRAC, reopened the question of whether or not the Guidelines should contain a list of organisms. The Working Group reaffirmed their earlier recommendation that ABRAC develop a list because

this would be of great help to researchers. Dr. MacKenzie asked if the list needed to be a part of the Guidelines or if it could be issued separately. Dr. Sederoff suggested it could be published as an appendix to the Guidelines. Dr. Vidaver commented that it would not be too difficult to come up with a list but that it was important that the list be flexible and that it should be able to be challenged through a public process. The Working Group reached consensus that the ABRAC develop a flexible list of each type of organism which could be expanded or contracted and that the list be presented through a mechanism which would allow for public debate.

Dr. Hafs asked the Working Group to develop examples for all four categories of organisms. The Working Group suggested the following examples, although they were regarded as preliminary, and subject to further review:

Type I. cattle
corn
rhizobium

Type 2. laboratory mice
sorghum
oats

Type 3. southern corn leaf blight
kudzu
water hyacinth

Type 4. foot and mouth disease
gypsy moth
corn lethal necrosis
Striga

Martha Steinbock
Rapporteur

Appendix I [as corrected]

II-B CLASSIFICATION OF ORGANISMS

II-B-1 Status 1. An organism with low potential for
a. transfer of genetic information to other spp.
b. rapid and widespread dissemination in the environment
c. uncontrollable reproduction
and has a history of domestication
and has non-pest or pathogen status

II-B-2 Status 2. An organism with some potential for
a. transfer of genetic information to other spp.
b. rapid and widespread dissemination in the environment
c. uncontrollable reproduction
or no history of domestication
or is generally recognized as having a predictable low consequence in the environment even though it may be a pest or pathogen

III-B-3 Status 3. An organism with 2 or more of the above traits

III-B-4 Status 4. An organism with 2 or more of the above traits and a pest or pathogen of high consequence

APPENDIX A

1. Status 1 Organisms.

Plants	Animals	Microorganisms
All major domesticated crop species except *Sorghum bicolor* *Solanum tuberosum*	All domesticated animals including: cattle, swine, sheep, horses, dogs, cats, mice, rats, Drosophila	*Azotobacter* spp. *Azospirillum* spp. *Bacillus subtilis* *B. thuringiensis* * *Bradyrhizobium* *Erwinia herbicola* * *Ps. fluorescens* * *Ps. syringae* * *Ps. putida* *Agrobacterium* *Radiobacter* *Trichoderma* spp.

* Rare strains have been reported to be pathogens under some conditions

Appendix I [as received]

II-B CLASSIFICATION OF ORGANISMS

II-B-1 Status 1. An organism with low potential for
a. transfer of genetic information to other spp.
b. rapid and widespread dissemination in the environment
c. uncontrollable reproduction
and has a history of domestication
and has non-pest or pathogen status

II-B-2 Status 2. An organism with some potential for
a. transfer of genetic information to other spp.
b. rapid and widespread dissemination in the environment
c. uncontrollable reproduction
or no history of domestication
or is generally recognized as having a predictable low consequence in the environment even though it may be a pest or pathogen

III-B-3 Status 3. An organism with 2 or more of the above traits

III-B-4 Status 4. An organism with 2 or more of the above traits and a pest or pathogen of high consequence

APPENDIX A

1. Status 1 Organisms.

Plants	Animals	Microorganisms
All major domesticated crop species except *Sorghum bicalor* *Solonum tuberosun*	All domesticated animals including: cattle, swine, sheep, horses, dogs, cats, mice, rats, Drosaphila	*Azotobacter* spp. *Azospirillum* spp. *Bacillus subtilis* *B. thurtugensis* * *Brady rhizobium* *Ercuinia herbicide* * *Ps. fluorescans* * *Ps. syringae* * *Ps. putida* *Agrobacterium* *Radiobacter* *Trichodeme* spp.

* Rare strains have been reported to be pathogens under some conditions

Appendix II

II-B CLASSIFICATION OF ORGANISMS

II-B-1 Status 1. An organism for which there is extensive biological knowledge, for example, domesticated organisms or organisms with a long history of use, which is not a pest or pathogen (except biocontrol agents) and which has a low potential for:

a) transfer of genetic information to other species
b) rapid and widespread dissemination in the environment
c) uncontrollable reproduction

such as cattle, corn, or rhizobium.

II-B-2 Status 2. An organism for which there is only some biological knowledge or is generally recognized as having a predictable low consequence in the environment though it may be a pest or pathogen and has some potential for:

a) transfer of genetic material to other species
b) rapid and widespread dissemination in the environment
c) uncontrollable reproduction

such as laboratory mice, sorghum, or oats.

III-B-3. An organism with two or more of the above traits and is a pest or pathogen of moderate consequence in the environment, such as southern corn leaf blight, kudzu, or water hyacinth.

II-B-4 An organism with one or more of the above traits and is a pest or pathogen of high consequence in the environment, such as foot and mouth disease, gypsy moth, corn lethal necrosis or Striga.

Streptococcus millerl
Streptococcus durans
Streptococcus mitior
Streptococcus ferus

Exceptions. Experiments described in Section III–A which require specific RAC review and NIH approval before initiation of the experiment.

Large-scale experiments (e.g., more than 10 liters of culture) require prior IBC review and approval (see Section III–B–5).

Experiments involving the deliberate cloning of genes coding for the biosynthesis of molecules toxic for vertebrates (see Appendix F).

Appendix C–VI—Footnotes and References of Appendix C

1. The original reference to organisms as Class 1, 2, 3, 4, or 5 refers to the classification in the publication *Classification of Etiologic Agents on the Basis of Hazard*, 4th Edition, July 1974; U.S. Department of Health, Education and Welfare, Public Health Service, Centers for Disease Control, Office of Biosafety, Atlanta, Georgia 30333.

The Director, NIH, with advice of the Recombinant DNA Advisory Committee, may revise the classification for the purposes of these Guidelines (see Section IV–C–1–b–(2)–(d)). The revised list of organisms in each class is reprinted in Appendix B to these Guidelines.

2. A subset of non-conjugative plasmid vectors are also poorly mobilizable (e.g., pBR322, pBR313). Where practical, these vectors should be employed.

3. Defined as observable under optimal laboratory conditions by transformation, transduction, phage infection, and/or conjugation with transfer of phage, plasmid, and/or chromosomal genetic information. Note that this definition of exchange may be less stringent than that applied to exempt organisms under Section III–D–4.

4. As classified in the Third Report of the International Committee on Taxonomy of Viruses: Classification and Nomenclature of Viruses, R.E.F. Matthews, Ed. Intervirology 12 (129–290) 1979.

5. i.e., the total of all genomes within a Family shall not exceed one-half of the genome.

Appendix D—Actions Taken Under the Guidelines

As noted in the subsections of Section IV–C–1–b–(1), the Director, NIH, may take certain actions with regard to the Guidelines after the issues have been considered by the RAC. Some of the actions taken to date include the following:

Appendix D–I

Permission is granted to clone foot and mouth disease virus in the EK1 host-vector system consisting of *E. coli* K–12 and the vector pBR322, all work to be done at the Plum Island Animal Disease Center.

Appendix D–II

Certain specified clones derived from segments of the foot and mouth disease virus may be transferred from Plum Island Animal Disease Center to the facilities of Genentech, Inc., of South San Francisco, California. Further development of the clones at Genentech has been approved under BL1+EK1 conditions.

Appendix D–III

The Rd strain of *Hemophilus influenzae* can be used as a host for the propagation of the cloned Tn 10 tet R gene derived from *E. coli* K–12 employing the non-conjugative *Hemophilus* plasmid, pRSF0885, under BL1 conditions.

Appendix D–IV

Permission is granted to clone certain subgenomic segments of foot and mouth disease virus in HV1 *Bacillus subtilis* and *Saccharomyces cerevisiae* host-vector systems under BL1 conditions at Genentech, Inc., South San Francisco, California.

Appendix D–V

Permission is granted to Dr. Ronald Davis of Stanford University to field test corn plants modified by recombinant DNA techniques under specified containment conditions.

Appendix D–VI

Permission is granted to clone in *E. coli* K–12 under BL1 physical containment conditions subgenomic segments of rift valley fever virus subject to conditions which have been set forth by the RAC.

Appendix D–VII

Attenuated laboratory strains of *Salmonella typhimurium* may be used under BL1 physical containment conditions to screen for the *Saccharomyces cerevisiae* pseudouridine synthetase gene. The plasmid YEp13 will be employed as the vector.

Appendix D–VIII

Permission is granted to transfer certain clones of subgenomic segments of foot and mouth disease virus from Plum Island Animal Disease Center to the laboratories of Molecular Genetics, Inc., Minnetonka, Minnesota, and to work with these clones under BL1 containment conditions. Approval is contingent upon review of data on infectivity testing of the clones by a working group of the RAC.

Appendix D–IX

Permission is granted to Dr. John Sanford of Cornell University to field test tomato and tobacco plants transformed with bacterial (*E. coli* K–12) and yeast DNA using pollen as a vector.

Appendix D–X

Permission is granted to Drs. Steven Lindow and Nickolas Panopoulos of the University of California, Berkeley, to release under specified conditions *Pseudomonas syringae* pv. *syringae* and *Erwinia herbicola* carrying *in vitro* generated deletions of all or part of the genes involved in ice nucleation.

Appendix D–XI

Agracetus of Middleton, Wisconsin, may field test under specified conditions disease resistant tobacco plants prepared by recombinant DNA techniques.

Appendix E—Certified Host-Vector Systems

(See also Appendix I)

While many experiments using *E. coli* K–12, *Saccharomyces cerevisiae* and *Bacillus subtilis* are currently exempt from the Guidelines under Section III–D–5, some derivatives of these host-vector systems were previously classified as HV1 or HV2. A listing of those systems follows:

Appendix E–I—Bacillus subtilis

HV1. The following plasmids are accepted as the vector components of certified *B. subtilis* HV1 systems: pUB110, pC194, pS194, pSA2100, pE194, pT127, pUB112, pC221, pC223, and pAB124. *B. subtilis* strains RUB 331 and BGSC 1S53 have been certified as the host component of HV1 systems based on these plasmids.

HV2. The asporogenic mutant derivative of *Bacillus subtilis*, ASB 298, with the following plasmids as the vector component: pUB110, pC194, pS194, pSA2100, pE194, pT127, pUB112, pC221, pC223, and pAB124.

Appendix E–II—Saccharomyces cerevisiae

HV2. The following sterile strains of *Saccharomyces cerevisiae*, all of which have the ste–VC9 mutation, SHY1, SHY2, SHY3, and SHY4. The following plasmids are certified for use: YIp1, YEp2, YEp4, YIp5, YEp8, YRp7, YEp20, YEp21, YEp24, YIp25, YIp26, YIp27, YIp28, YIp29, YIp30, YIp31, YIp32, and YIp33.

Appendix E–III—Escherichia coli

EK2 Plasmid Systems. The *E. coli* K–12 strain chi–1776. The following

plasmids are certified for use: pSC101, pMB9, pBR313, pBR322, pDH24, pBR325, pBR327, pGL101, and pHB1. The following *E. coli/S. cerevisiae* hybrid plasmids are certified as EK2 vectors when used in *E. coli* chi-1776 or in the sterile yeast strains, SHY1, SHY2, SHY3, and SHY4: YIp1, YEp2, YEp4, YIp5, YEp6, YRp7, YEp20, YEp21, YEp24, YIp25, YIp28, YIp27, YIp28, YIp29, YIp30, YIp31, YIp32, and YIp33.

EK2 Bacteriophage Systems. The following are certified EK2 systems based on bacteriophage lambda:

Vector	*Host*
λgt*WES*·λB'	DP50*supF*
λgt *WES*λB*	DP50*supF*
λgt 7.1 *vir*λB'	*E. coli* K-12
λgtλALO·λB	DP50*supF*
Charon 3A	DP50 or DP50*supF*
Charon 4A	DP50 or DP50*supF*
Charon 16A	DP50 or DP50*supF*
Charon 21A	DP50*supF*
Charon 23A	DP50 or DP50*supF*
Charon 24A	DP50 or DP50*supF*

E. coli K-12 strains chi-2447 and chi-2281 are certified for use with lambda vectors that are certified for use with strain DP50 or DP50*supF* provided that the su⁻ strain not be used as a propagation host.

Appendix E-IV—Neurospora crassa

HV1. The following specified strains of *Neurospora crassa* which have been modified to prevent aerial dispersion:

Inl (inositolless) strains 37102, 37401, 46316, 64001, and 89601.

Csp-1 strain UCLA37 and csp-2 strains FS 590, UCLA101 (these are conidial separation mutants).

Eas strain UCLA191 (an "easily wettable" mutant).

Appendix E-V—Streptomyces

HV1. The following *Streptomyces* species: *Streptomyces coelicolor, S. lividans, S. parvulus,* and *S. griseus.* The following are accepted as vector components of certified *Streptomyces* HV1 systems: *Streptomyces* plasmids SCP2, SLP1.2, pIJ101, actinophage phi C31, and their derivatives.

Appendix E-VI—Pseudomonas putida

HV1. Pseudomonas putida strains KT2440 with plasmid vectors pKT262, pKT263, and pKT264.

Appendix F—Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates

Appendix F-I—General Information.

Appendix F specifies the containment to be used for the deliberate cloning of genes coding for the biosynthesis of molecules toxic for vertebrates. The cloning of genes coding for molecules toxic for vertebrates that have an LD_{50} of less than 100 nanograms per killogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, *Shigella dysenteriae* neurotoxin) is covered under Section III-A-1 of the Guidelines and requires RAC review and NIH and IBC approval before initiation. No specific restrictions shall apply to the cloning of genes if the protein specified by the gene has an LD_{50} of 100 micrograms or more per kilogram of body weight. Experiments involving genes coding for toxic molecules with an LD_{50} of 100 micrograms or less per kilogram body weight shall be registered with ORDA prior to initiating the experiments. A list of toxic molecules classified as to LD_{50} is available from ORDA. Testing precedures for determining toxicity of toxic molecules not on the list are available from ORDA. The results of such tests shall be forwarded to ORDA which will consult with the RAC Working Group on Toxins prior to inclusion of the molecules on the list (see Section IV-C-1-b-(2)-(e)).

Appendix F-II—Containment Conditions for Cloning of Toxic Molecule Genes in E. coli K-12

Appendix F-II-A. Cloning of genes coding for molecules toxic for vertebrates that have an LD_{50} in the range of 100 nanograms to 1000 nanograms per kilogram body weight (e.g., abrin, *Clostridium perfringens* epsilon toxin) may proceed under BL2+EK2 or BL3+EK1 containment conditions.

Appendix F-II-B. Cloning of genes for the biosynthesis of molecules toxic for vertebrates with an LD_{50} in the range of 1 microgram to 100 micrograms per kilogram body weight may proceed under BL1+EK1 containment conditions (e.g., *Staphylococcus aureus* alpha toxin, *Staphylococcus aureus* beta toxin, ricin, *Pseudomonas aeruginosa* exotoxin A, *Bordatella pertussis* toxin, the lethal factor of *Bacillus anthracis,* the *Pasteurella pestis* murine toxins, the oxygen-labile hemolysins such as streptolysin O, and certain neurotoxins present in snake venoms and other venoms).

Appendix F-II-C. Some enterotoxins are substantially more toxic when administered enterally than parenterally. The following enterotoxins shall be subject to BL1+EK1 containment conditions: cholera toxin, the heat labile toxins of *E. coli, Klebsiella,* and other related proteins that may be identified by neutralization with an antiserum monospecific for cholera toxin, and the heat stable toxins of *E. coli* and of *Yersinia enterocolitica.*

Appendix F-III—Containment Conditions for Cloning of Toxic Molecule Genes in Organisms Other Than E. coli K-12

Requests involving the cloning of genes coding for molecules toxic for vertebrates in host-vector systems other than *E. coli* K-12 will be evaluated by ORDA which will consult with the Working Group on Toxins (see Section IV-C-1-b-(3)-(f)).

Appendix F-IV—Specific Approvals

Appendix F-IV-A. Permission is granted to clone the Exotoxin A gene of *Pseudomonas aeruginosa* under BL1 conditions in *Pseudomonas aeruginosa* and in *Pseudomonas putida.*

Appendix F-IV-B. The pyrogenic exotoxin type A (Tox A) gene of *Staphylococcus aureus* may be cloned in an HV2 *Bacillus subtilis* host-vector system under BL3 containment conditions.

Appendix F-IV-C. Restriction fragments of *Corynephage Beta* carrying the structural gene for diphtheria toxin may be safely cloned in *e. coli* K-12 in high containment Building 550 at the Frederick Cancer Research Facility. Laboratory practices and containment equipment are to be specified by the IBC. If the investigators wish to proceed with the experiments, a prior review will be conducted to advise NIH whether the proposal has sufficient scientific merit to justify the use of the NIH BL4 facility.

Appendix F-IV-D. The genes coding for the *Staphylococcus aureus* determinants, A, B, and F, which may be implicated in toxic shock syndrome may be cloned in *E. coli* K-12 under BL2+EK1 conditions. The *Staphylococcus aureus* strain used as the donor is to be alpha toxin minus. It is suggested that, if possible, the donor *Staphylococcus aureus* strain should lack other toxins with LD_{50}s in the range of one microgram per kilogram body weight such as the exfoliative toxin.

Appendix F-IV-E. Fragments F-1, F-2 and F-3 of the diphtheria toxin gene (tox) may be cloned in *E. coli* K-12 under BL1+EK1 containment conditions and may be cloned in *Bacillus subtilis* host-vector systems under BL1 containment conditions. Fragment F-1 and fragment F-2 both contain: (i) Some or all of the transcriptional control elements of *tox;* (ii) the signal peptide; and (iii) fragment A (the center responsible for ADP-ribosylation of elongation factor 2). Fragment F-3 codes for most of the non-toxic fragment B of the toxin and contains no sequences coding for any portion of the enzymatically active fragment A moiety

☆U. S. GOVERNMENT PRINTING OFFICE:1989-241-859:00087/CSR5